REMARKS

Upon entry of the foregoing amendment, claims 14, 16-20, and 28-36 are pending in the application, with 14, 29, and 36 being the independent claims. Claims 20 and 35 have been withdrawn by the Examiner.

Based on the following remarks, Applicants respectfully request that the Examiner reconsider all outstanding objections and rejections and that they be withdrawn.

Interview Summary

Applicants appreciate the courtesies that were extended by Examiner Chen to Applicants' undersigned representative during the telephone interview on September 7, 2010 and the follow-up interview on September 13, 2010. Applicants concur that the Interview Summary mailed September 10, 2010 accurately reflects the substance of the telephonic interview. Applicants further note that the Examiner agreed on September 13, 2010 to hold another telephonic interview with Applicants and the Examiner's supervisor after the present response was filed.

Rejections Under 35 U.S.C. § 103

Claims 14, 16-19, and 28-34 and 36 have been rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable over Takesako *et al.* in view of Lenney *et al.* (Office Action, page 3). Applicants respectfully traverse this rejection.

The Examiner alleges that Takesako *et al.* teaches the use of antifungal and antimicrobial agents with a fungal immunogen vaccine but does not teach a composition comprising compound 48/80. (Office Action, page 3). The Examiner further alleges that Lenney *et al.* teaches the antimicrobial activity of compound 48/80. The Examiner is of the opinion that it would have been obvious to one of ordinary skill in the art to use compound 48/80 as the antimicrobial agent in the vaccine composition of Takesako *et al.*, motivated to do so to provide antimicrobial protection to the vaccine. (Office Action, pages 3-4). The Examiner alleges that one would have a reasonable expectation of success because the addition of antimicrobial agents to pharmaceutical products is routinely practiced. (Office

Action, page 4). The Examiner acknowledges that neither Takesako *et al.* nor Lenney *et al.* teach that compound 48/80 is useful as an adjuvant or that the compound will enhance the immune response to an immunogen. (Office Action, page 4). However, the Examiner states that the actual steps of administering an immunogen with compound 48/80 are suggested in the prior art and one carrying out the steps would have necessarily achieved the adjuvant effect that Applicants assert is novel. (Office Action, page 4).

Applicants respectfully disagree. The Supreme Court has articulated that obviousness under § 103(a) is determined by an analysis of the following factors: (1) the scope and content of the prior art; (2) the differences between the prior art and the claims at issue; (3) the level of ordinary skill in the art at the time the invention was made; and (4) objective evidence of nonobviousness. *Graham v. John Deere Co.*, 383 U.S. 1, 17 (1966). The obviousness or nonobviousness of the subject matter is to be determined based on these considerations however, secondary considerations such as commercial success, long-felt but unresolved needs and the failure of others can be utilized to determine the circumstances surrounding the origin of the invention. *See KSR Int'l Co. v. Teleflex Inc.*, 127 S.Ct. 1727, 1730 (2007). If such secondary considerations exist, they must be considered. *See Stratoflex, Inc. v. Aeroquip Corp.*, 713 F.2d 1530, 1538-1539 (Fed. Cir. 1983).

In *KSR*, the Supreme Court also made clear that predictable variations are likely obvious, but unpredictable variations are not:

> If a person of ordinary skill can implement a predictable variation, §103 likely bars its patentability. For the same reason, if a technique has been used to improve one device, and a person of ordinary skill in the art would recognize that it would improve similar devices in the same way, using the technique is obvious unless its actual application is beyond his or her skill. *Sakraida* and *Anderson's-Black Rock* are illustrative - a court must ask whether the improvement is more than the predictable use of prior art elements according to their established functions.

KSR at 1740.

The Court also recognized that when the prior art taught away from the claimed invention, the invention was more likely to be non-obvious: "when the prior art teaches away

from combining certain known elements, discovery of a successful means of combining them is more likely to be nonobvious." *KSR* at 1740 (citing *United States v. Adams*, 383 U.S. 39, 51-52 (1996)).

The Court also emphasized the importance of identifying "a reason" that a person of ordinary skill in the relevant field would have combined the elements in the fashion claimed by the new invention. *Id.* at 1731. The Court also emphasized that this analysis should be made explicit:

> Often it will be necessary for a court to look to interrelated teachings of multiple patents; the effects of demands known to the design community or present in the marketplace; and the background knowledge possessed by a person having ordinary skill in the art, all in order to determine whether there was an apparent reason to combine the known elements in the fashion claimed by the patent at issue. To facilitate review, this analysis should be made explicit.

Id. at 1740-1741 (citing *In re Kahn*, 441 F.3d 977, 988 (Fed. Cir. 2006)).

The present invention is directed to a method of inducing an immune response (claim 14), a method of enhancing a protective immune response to an immunogen (claim 29), or a method of providing adjuvant activity to an immunogen (claim 36), comprising concurrently administering an immunogen and compound 48/80 to a subject in an amount effective to produce an immune response therein, wherein the compound 48/80 is administered in an adjuvant-effective amount and wherein the immunogen and the compound 48/80 are administered simultaneously in a common pharmaceutical carrier.

Takesako *et al.* is directed to fungal antigens that can be used as part of a vaccine or to suppress allergic reactions (abstract). Takesako *et al.* states that

> [t]he vaccine composition of the present invent may be used in combination with antifungal agents, such as fluconazole and amphotericin B, and β-lactam antibiotics and other various antibacterial antimicrobial agents. The vaccine composition of the present invention exhibits an additively or geometrically enhanced effectiveness when used in combination with an antifungal agent.

(paragraph [0148]). Notably, Takesako *et al.* does not mention compound 48/80, either as an antimicrobial agent or as an adjuvant.

Lenney *et al.* teaches that compound 48/80 has moderate antimicrobial activity against protozoa, bacteria, and fungi (Table 1). Lenney *et al.* points out that one of the least sensitive organisms tested is the fungus *Aspergillus niger* (page 703, column 2). Lenney *et al.* further points out that compound 48/80 is actually a complex mixture of polymers and that fractionation of compound 48/80 only partially separates the antimicrobial activity from the histamine-releasing activity (page 703, column 2 to page 704, column 1).

The present claims require that an adjuvant-effective amount of compound 48/80 be administered to a subject. Neither Takesako *et al.* nor Lenney *et al.* provide any teaching or suggestion that compound 48/80 has adjuvant activity. One of ordinary skill in the art reading the cited references would not have been aware of any adjuvant activity and could not know an adjuvant effect could be obtained with a sufficient amount of compound 48/80. Thus, it could not have been obvious to the ordinary skilled artisan to carry out a method in which an adjuvant-effective amount of compound 48/80 is used.

The Examiner states that "[i]f one of ordinary skill in the art were to carry out the steps of administering Compound 48/80 with an immunogen, as suggested by Takesako in combination with Lenney, one would have necessarily achieved the adjuvant effect that Applicant asserts is novel." (Office Action, page 4). Applicants respectfully disagree. The Examiner's statement would only be true if compound 48/80 has adjuvant activity at any dose. In fact, the present inventors have shown that a sufficient dose of compound 48/80 is required to have an adjuvant effect and administration of a dose lower than the sufficient dose leads to an absence of an adjuvant effect. This is disclosed in a publication from Applicants' laboratory (McGowen *et al.*, Vaccine 27:2544 (2009)), attached hereto as **Exhibit A**. This reference describes an experiment involving intradermal delivery to mice of a recombinant anthrax protective antigen (rPA) in combination with increasing doses of compound 48/80 (page 3546, column 1, section 3.1). McGowen *et al.* discloses that a 3 μg dose of compound

48/80 was insufficient to elicit any adjuvant effect while doses of 10 μg and 30 μg increased anti-rPA IgG subclass antibody levels 53- and 177-fold respectively (Figure 2). As the mice in the experiment weigh about 20 g each, the 3 μg dose corresponds to a dose of about 150 μg/kg body weight while the 10 μg dose corresponds to a dose of about 500 μg/kg body weight. Thus, it is clear that not all doses of compound 48/80 constitute an adjuvant effective amount as required by the present claims. The Examiner's assertion that administering compound 48/80 with an immunogen would necessarily elicit an adjuvant effect is incorrect. If an outcome or consequence is not necessarily present in a composition allegedly suggested by the prior art, a *prima facie* case of obviousness has not been made.

It is noted that Lenney *et al.* tested compound 48/80 for its antimicrobial effect at concentrations of 0.1-100 μg/ml in culture medium (page 704, Table I). The concentrations effective on microorganisms in a culture dish do not translate directly to an effective concentration in a pharmaceutical composition. Lenney *et al.* does not provide any guidance on using compound 48/80 as an antimicrobial agent in a pharmaceutical composition. Thus, one of ordinary skill in the art reading Lenney *et al.* would not necessarily prepare a pharmaceutical composition comprising a dose of compound 48/80 that is an adjuvant-effective amount. For example, in an average 70 kg human subject, the dose of compound 48/80 equivalent to the 10 μg dose (500 μg/kg body weight) demonstrated in McGowen *et al.* to be effective in a mouse would be 35,000 μg. Considering that the highest concentration of compound 48/80 tested by Lenney *et al.* is 100 μg/ml, it is highly unlikely that one of ordinary skill in the art would use 35,000 μg of compound 48/80 as an antimicrobial agent in a pharmaceutical composition for administration to a human subject. Thus, the ordinary skilled artisan reading Lenney *et al.* would not necessarily prepare a composition comprising an adjuvant-effective amount of compound 48/80. Again, the Examiner's assertion that administering compound 48/80 as an antimicrobial agent with an immunogen would necessarily elicit an adjuvant effect is incorrect.

The fact that a certain result or characteristic may occur or be present in the prior art is not sufficient to establish the inherency of that result or characteristic. *In re Rijckaert*, 9 F.3d

1531, 1534, 28 USPQ2d 1955, 1957 (Fed. Cir. 1993); *In re Oelrich*, 666 F.2d 578, 581-82, 212 USPQ 323, 326 (CCPA 1981). "To establish inherency, the extrinsic evidence 'must make clear that the missing descriptive matter is necessarily present in the thing described in the reference, and that it would be so recognized by persons of ordinary skill. Inherency, however, may not be established by probabilities or possibilities. The mere fact that a certain thing may result from a given set of circumstances is not sufficient.' " *In re Robertson*, 169 F.3d 743, 745, 49 USPQ2d 1949, 1950-51 (Fed. Cir. 1999). Here, the presence of an adjuvant effective amount of compound 48/80 in a compositions does not necessarily flow from a combination of the teachings of Takesako *et al.* and Lenney *et al.* Furthermore the M.P.E.P. (2141.02(V)) explicitly states that obviousness cannot be predicated on what is not known at the time an invention is made, even if the inherency of a certain feature is later established. *In re Rijckaert*, 9 F.2d 1531, 28 USPQ2d 1955 (Fed. Cir. 1993). Thus, the obviousness rejection is improper.

The Examiner alleges that one of ordinary skill in the art would have been motivated to add an antimicrobial agent to the vaccine of Takesako *et al.* to provide antimicrobial protection to the vaccine and that one would have had a reasonable expectation of success because the addition of antimicrobial agents to pharmaceutical products is routinely practiced. (Office Action, page 3).

Applicants respectfully disagree. While antimicrobial agents may often be present in pharmaceutical products, the cited references provide no incentive to one of ordinary skill in the art to use compound 48/80 in such a capacity. Thousands (if not tens of thousands) of agents with at least a small amount of antimicrobial activity were known at the time the present invention was made. There is nothing in the cited art or general knowledge in the art delineated by the Examiner to show why one of ordinary skill in the art would have been motivated to select compound 48/80 out of the thousands of known antimicrobial agents.

Furthermore, compound 48/80 has properties that make it highly undesirable as a pharmaceutical excipient for its antimicrobial activity or any other activity. Compound 48/80 has strong mast cell degranulation activity, leading to release of histamine and resulting in

inflammatory reactions (present specification, page 2, lines 4-16). Clearly, this is an activity that is not desirable for an excipient in a pharmaceutical product. Moreover, compound 48/80 is a complex mixture of unknown components, each component having unknown activities. This complexity is evidenced by the inability of Lenney *et al.* to completely separate the antimicrobial activity of compound 48/80 from the histamine-releasing activity. This lack of understanding of the structural and functional nature of compound 48/80 is undesirable for an excipient in a pharmaceutical product. Additionally, Lenney *et al.* teaches that compound 48/80 has only moderate antimicrobial activity against organisms in general, and that some common microorganisms (*A. niger* and *K. pneumoniae*) were more resistant. Neither Takesako *et al.* nor Lenney *et al.* provide any reason or incentive, particularly in light of the undesirable factors recited above, to select compound 48/80 to protect a vaccine composition out of all of the potential antimicrobial agents known in the art, as is suggested by the Examiner.

The Examiner's suggestion that any antimicrobial agent would reasonably be expected to function to provide antimicrobial protection to the vaccine also ignores that fact that an antimicrobial agent may have a detrimental effect on the immune response induced by the vaccine composition. For example, Fernandez *et al.*, J. Infect. Dis. 190:1762 (2004) (attached hereto as **Exhibit B**) discloses that inclusion of the antibiotic azithromycin in a pneumococcal conjugate vaccine inhibits the immune response to the vaccine. Thus, the statement that all antimicrobial agents can be used in a vaccine composition is incorrect.

The Examiner may be suggesting that it would have been obvious to try any antifungal or antimicrobial agent in combination with the fungal vaccine of Takesako *et al.* Applicants respectfully disagree. Applicants point out that the Examination Guidelines for Determining Obviousness state that even if one were to consider that the teachings of the prior art rendered the presently claimed invention "obvious to try, " such a rationale must include 1) a finding that at the time of the invention, there had been a recognized problem or need in the art; 2) a finding that there had been a finite number of identified, predictable potential solutions to the recognized need or problem; and 3) a finding that one of ordinary

skill in the art could have pursued the known potential solutions with a reasonable expectation of success (see, *e.g.*, page 57529, first column and page 57532, first through third columns).

If, for the sake of argument, one of ordinary skill in the art reading the cited references were to define the problem to be solved to be the selection of an effective antifungal or antimicrobial agent for use in combination with a fungal vaccine to enhance the efficacy of the vaccine, such an ordinary skilled artisan would have to conclude that the number of identified, predictable potential solutions to this problem, according to what the cited references provide, is not finite at all. At the time of filing of the present application, one was aware of thousands of possible antifungal and antimicrobial agents. Such an ordinary skilled artisan would have to choose from an extremely large number of possible solutions in order to identify any particular agent that would solve the "problem" as described herein. It is apparent that the presently claimed compound 48/80 could not be considered to be included among "a finite number of identified, predictable, potential solutions" as set forth in the Examination Guidelines. Therefore the claims would not have been obvious at the time this invention was made. Thus, the present rejection is believed to be overcome and its withdrawal is respectfully requested.

Applicants also point to *Takeda Chemicals Industries, Ltd. v. Alphapharm Pty. Ltd.*, 492 F.3d 1350, 83 U.S.P.Q.2d 1169 (Fed. Cir. 2007) as relevant to the present claims. The *Takeda* court upheld a finding of non-obviousness of claims directed to a genus of chemical compounds for use in treating diabetes. In challenging the argument that the knowledge of prior art compounds and techniques rendered the claims "obvious to try," the court pointed out that "[r]ather than identify predictable solutions for antidiabetic treatment, the prior art disclosed a broad selection of compounds any one of which could have been selected as a lead compound for further investigation." *Id.* at 1359.

Similar to the genus of chemical compounds in *Takeda*, the prior art discloses information about a large variety of antifungal and antimicrobial agents. These disclosures would result in a very broad selection of chemical structures, any one of which could have

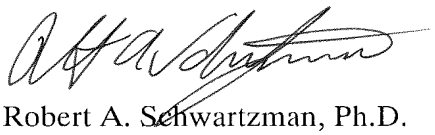
been selected for further investigation. Thus, the case law supports Applicants' position that the invention as claimed herein could not have been obvious at the time this invention was made.

It is respectfully requested that the rejection of claims 14, 16-19, and 28-34 and 36 under 35 U.S.C. § 103(a) be withdrawn.

CONCLUSION

Accordingly, Applicant submits that the present application is in condition for allowance and the same is earnestly solicited. The Examiner is encouraged to telephone the undersigned at 919-854-1400 for resolution of any outstanding issues.

Respectfully submitted,



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